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Scale-down and initial characterization studies of an allogeneic cell therapy manufacturing process

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CELL CULTURE APPROACHES FOR T-CELL CANCER IMMUNOTHERAPIES

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Cancer therapies leveraging the immune system have been improving the course of disease. T-cell therapies are one of the modalities of immune therapy, which also include small molecules, proteins, and various types of immune cells. T-cell therapies include T-cell Receptor cells (TCR), Chimeric Antigen Receptor (CAR) T-cells, and Cytotoxic T-Lymphocytes (CTL). Although the nascent cell therapy industry faces many manufacturing challenges, it benefits from the vast experience of the blood industry and cell-produced biologics industry.

A notable manufacturing challenge for most T-cell therapies results from their autologous nature, in which cells from a patient are used to produce the therapeutic cells for the same patient. The resultant patient-specific manufacture introduces new challenges to scale-out throughout the process, particularly for cell culture. In common with classic therapeutic protein scale-out approaches, a large number of small-scale cultures must be run simultaneously at the commercial stage. However, patient-specific cell therapies require that each culture is performed using cells from the patient to be treated and is adequately separated from others to prevent cross-contamination. Further, the cultures behave differently for each patient due to the differences in the starting patient-derived cell seed. Finally, T-cell growth is typically induced by an activation step (via specific antigens or non-specific activation signaling). Accordingly, a culture stage allowing undisturbed cellular interactions at the initiation of T-cell cultures is required.

A number of approaches are available to address the challenges of cost-effective culture scale-out for T-cell therapies. These approaches include GMP culture platforms from the therapeutic protein and blood industries. Platforms using disposable cell contact surfaces are predominantly favored to minimize the risk of cross-contamination and to provide rapid turnover between patient-batches. Rocking platform bioreactors such as the WAVE have been extensively used for T-cell cultures due to simplicity and ease of closed-system manipulations. However, the need for undisturbed cell-cell interactions to achieve T-cell activation early in the culture demands static seed trains in another platform. Static cultures based on gas-permeable vessels that require minimal operator preparation are also widely used. One example is gas-permeable culture bags filled using closed-system weld connections. Another example is the Gas-permeable Rapid Expansion (G-Rex) device, a static culture vessel in which the cells rest on a gas permeable surface. In this device, excellent membrane permeability allows high densities of cells to grow on the bottom of the vessel. Further, the passive gas exchange at the bottom of the vessel allows large amounts of medium to be placed into the vessel without compromising gas exchange. This allows long-term cultures with little need for medium exchange, if any. We compare cultures in G-Rex, gas-permeable bags, and the WAVE bioreactor to demonstrate that all produce sufficient cell expansion with appropriate cell characteristics. However, some T-cell immunotherapies may have particular culture needs that favor one platform over the others. In addition, we observe activation in static cultures and characterize the undisturbed time necessary. We illustrate examples of scale-out for each culture platform and discuss consequences. Finally, we generate models to compare projected commercial costs of the culture platforms. Together, our studies illustrate three disposable culture systems that have the potential to enable commercialization of multiple types of T-cell therapies.